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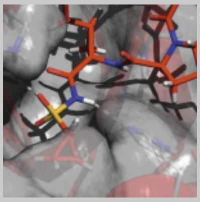

International Year of the Periodic Table 2019: Elements important for Life Sciences

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Ruthenium – A Non-essential Element that May Become Essential in Treating Chemoresistant Cancers

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In 1844, prior to Dmitry Mendeleev conceiving the Periodic Table of the Elements, a fellow Russian by the name of Karl Ernst Claus working in Kazan discovered ruthenium and named it after the Latin name for his homeland, Ruthenia. As the elements were placed in the Periodic Table, ruthenium found its home as a second row transition metal, nestled between technetium and rhodium, below iron and above osmium. Like its neighbors, ruthenium has found many important applications, both in its elemental form, *i.e.* in alloys, and due to the rich and diverse coordination chemistry it displays across a range of oxidation states (from –2 to +8). Ruthenium compounds span mononuclear complexes through to the bulk metal, with a wealth of discrete molecular clusters and nanoscale ruthenium materials.

Perhaps the best known application of ruthenium complexes is as alkene metathesis catalysts, with the quintessential complexes being Grubbs' first and second generation catalysts (Fig. 1a and b).[1] Now a huge range of ruthenium-based alkene metathesis catalysts are available and are employed in the synthesis of complex molecules. Many other important transformations are catalyzed by ruthenium complexes,[2] such as ruthenium(II)-arene complexes with chiral diamine co-ligands (Fig. 1c), pioneered by Noyori, that catalyze transfer hydrogenation reactions with very high enantioselectivities.[3] Although considerably more active ruthenium-based transfer hydrogenation catalysts have since been developed,[4] recently it was shown that these complexes catalyze the transfer hydrogenation of coenzyme NAD^+ to NADH in cells in the presence of non-toxic doses of formate. The ensuing reductive stress leads to cell death.[5] Indeed, the prospect of using metal-based catalysts as drugs represents a tantalizing prospect as miniscule doses of the compound can potentially be applied and a number of small molecule metal catalyst enzyme mimics are progressing through clinical trials.[6]

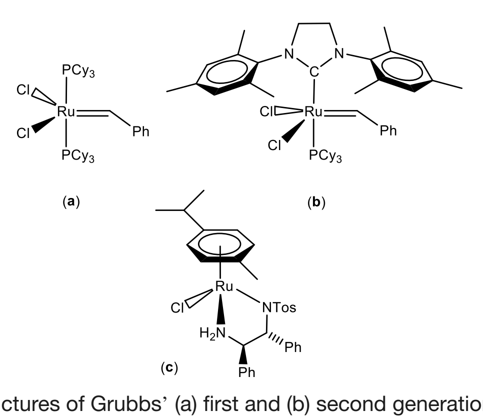

Fig. 1. Structures of Grubbs' (a) first and (b) second generation catalysts and (c) an example of a Noyori-type catalyst.

While the prospect of using an abiotic catalytic process to treat cancer is still in its infancy, ruthenium photocatalysts have been extensively evaluated in medicine as photosensitizers[7] and one compound has progressed to clinical trials (see below). Related ruthenium complexes are also extensively used in dye-sensitized solar cells.[8]

Interest in the medicinal properties of ruthenium compounds emanated from the paradigm changing success of cisplatin used in the treatment of a range of cancers following its clinical approval 41 years ago.[9] At that time cisplatin was perceived to be a wonder drug, and with DNA as the target it was active against a broad range of cancers, and remains a bedrock in cancer therapy to this day.[10] Nonetheless, limitations of cisplatin and subsequent approved platinum-based drugs that gained clinical approval ignited interest in ruthenium complexes as it was thought that they could overcome the limitations of the approved platinum-centered drugs, *i.e.* drug resistance and high general toxicity. It was found that ruthenium compounds are generally better tolerated. The basic premise for this better tolerance is that the body is well adapted to both store and transport iron species and, therefore, since ruthenium is found directly below iron in the Periodic Table, it might be handled using the innate system evolved to process iron.[11] The two elements share close structural similarities, but their function is quite distinct. Moreover, as rapidly growing cancer cells tend to sequester large amounts of iron, then by hijacking the iron delivery system, ruthenium complexes should be preferentially delivered to cancer cells relative to healthy cells. More generally, iron is naturally present in many proteins and many ruthenium compounds also have a binding preference for proteins, which contrasts with the behavior of platinum-based drugs. Since ruthenium compounds generally exhibit octahedral or pseudo-octahedral geometries they are also endowed with a greater degree of selectivity compared to structurally simpler square planar platinum compounds. A key goal, however, is to control binding of ruthenium complexes to specific, cancer-related proteins.

The ruthenium(III) complex KP1019 (Fig. 2a), which is steadily progressing through clinical trials, was selected, in part, on its ability to bind to the iron binding site in lactoferrin (used as a model for transferrin), and accumulate in tumors.[12] In a phase I clinical study KP1019 showed promising anticancer activity accompanied by only modest (manageable) side-effects.[13] A phase I clinical trial of a related ruthenium(III) compound, NAMI-A (Fig. 2b), also resulted in disease stabilization.[14] However, in a phase I/II trial combining NAMI-A with gemcitabine, for the treatment of non-small cell lung cancer, the combination was less effective than gemcitabine treatment alone.[15]

Ruthenium(II) complexes also exhibit promising anticancer properties. Although at a less advanced stage of development than the ruthenium(III) compounds mentioned above, RAPTA-C and RAPTA-T (see Fig. 2c for RAPTA-C, in RAPTA-T a toluene ring replaces the p-cymene ring in RAPTA-C), which are not cytotoxic to cells, display potent and synergistic activity when used in combination with cytotoxic agents,[16] sensitizing even chemoresistant tumors such that they respond to chemotherapy.[17] While the mode of action of these ruthenium(II) compounds is under study an epigenetic mechanism has been identified with accumulation on the nucleosome core particles in chromatin.

Such binding elicits a major allosteric effect in the histone core leading to binding of other agents at distant sites from the RAPTA binding site.[18] The most advanced ruthenium(II) complex is TLD1433 (Fig. 2d), a photosensitizer that recently entered clinical trials for non-muscle invasive bladder cancer.[19] The results of the trial appear to be highly promising and phase II clinical trials should follow, with potentially a broader range of cancers evaluated.

In conclusion, over one quarter of the elements are employed in clinically approved chemotherapy and biomedical imaging applications, and there is a good chance that ruthenium will soon join them.

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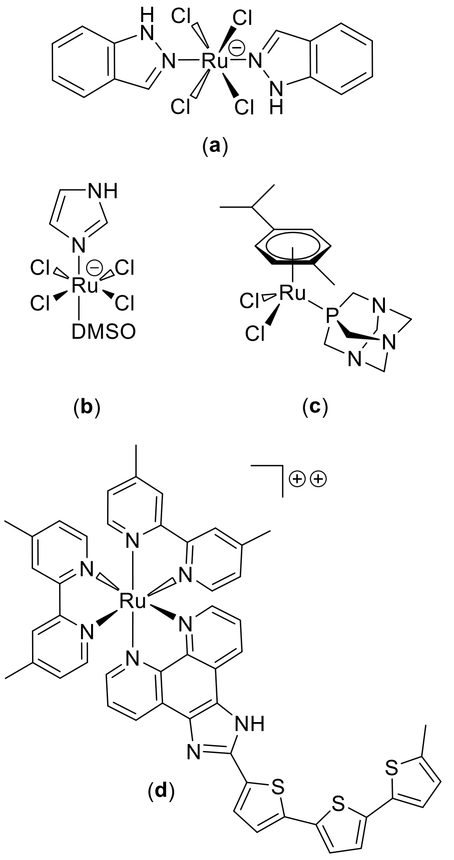

Fig. 2. Structures of (a) KP1019, (b) NAMI-A, (c) RAPTA-C and (d) TLD1433. Note that counter ions are omitted for clarity.

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